Iron in Biology

Vincenzo Abbate and Robert Hider

The role of iron in biology is enormous and this themed metallomics publication does not aim to be comprehensive, but rather to concentrate and highlight some unresolved issues, as well as recent advances in the field. There are many overviews on various aspects of iron biology [1-4].

This themed issue is organised into six distinct sections, covering aspects of iron cluster dynamics and iron protein mechanisms; also included are sections on bacterial, plant and mammalian iron biology, and the increasingly important subject of iron-associated diseases.

Iron Cluster Dynamics

DNA repair enzymes, including helicases, nucleases, glycolases and demethylases, are dependent on iron acting as an essential cofactor. Furthermore, iron-sulfur clusters are critical for the activity of DNA polymerase. Clearly the levels of labile iron in the nucleus are critical for optimal DNA metabolism. Sergi Puig *et al.* (DOI: 10.1039/c7mt00116a) review many of these important issues in a well referenced contribution. A DNA charge transport model is presented which indicates how iron-sulfur clusters are critical for both the detection and the repair of DNA mismatches along the genome. The cytosolic iron-sulfur cluster assembly system (CIA) biosynthesizes iron-sulfur clusters for both cytosolic and nuclear proteins. Amanda Vo *et al.* (DOI: 10.1039/c7mt00181a) describe some of the terminal steps of this process in yeast. Despite considerable progress in our understanding of iron-sulfur cluster biosynthesis, it is still not clear how iron is incorporated into such clusters. Glutaredoxins are involved in iron-sulfur cluster synthesis and Adrienne Dlouhy *et al.* (DOI: 10.1039/c7mt00144d) describe how Grx-4 controls this process through a bridging [2Fe – 2S] cluster. Moreover, Galeano *et al.* (DOI: 10.1039/c7mt00089h) propose the involvement of frataxin in this process and describe how it regulates the oligomerization of the scaffold protein. They also indicate a possible role for zinc in the mechanism. As our knowledge is extended with regards to the ever widening role of iron-sulfur clusters, their central role in so many biological processes is becoming clearer.

Iron Protein Mechanisms

The architecture of iron-dependent enzymes and proteins is diverse and many involve subtle conformational changes. Ferritin is one such protein which is present in various modifications in most life forms. Although extensively studied over the past 50 years, there is still disagreement on its mechanism of action. Wilfred Hagen *et al.* (DOI: 10.1039/ c7mt00124j)

discuss in detail five current issues, many of them focusing on the ferroxidase center. Justin Bradley *et al.* (DOI: 10.1039/c7mt00187h) discuss in detail how tyrosine and tryptophan transfer electrons between the central cavity iron and the ferroxidase site in bacterioferritin. They suggest that the ferrioxidase site is surrounded by a network of aromatic residues, which together facilitate the redox cycling of the di-iron site during mineralisation. Sunanda Williams and Dipankar Chatterji (DOI: 10.1039/c7mt00008a) describe a similar iron storage protein isolated from *Mycobacterium smegmatis* and suggest that the surface aspartate residues facilitate the movement of iron(II) cations in a similar fashion to that of ion movement through a transmembrane pore. Guangyu Wang (DOI: 10.1039/c7mt00065k), working with the cystic fibrosis transmembrane conductance regulator (CFTR) anion channels, has demonstrated an unexpected interplay between CO and iron(III) which could have a wide relevance to transmembrane channel phenomena. Frataxin interaction with both copper(II) and iron(II) is reported by Han *et al.* (DOI: 10.1039/c7mt00031f) who suggest that there could be a functional role for frataxin not only for iron, but also for copper.

Bacterial Iron Transport

This themed issue includes aspects relating to iron uptake, iron efflux and iron storage in bacteria. Microbiological studies have provided many insights into the general aspects of iron biology over the past 50 years, this being particularly true for iron absorption. Reitz, Sandy and Butler (DOI: 10.1039/c7mt00111h) provide an exhaustive review on the biosynthesis of catechol siderophores. The authors point out that a number of factors limit enterobactin effectiveness, although it being a "seemingly perfect iron(III) chelator". They go on to indicate how members of an enterobactin-based bio-combinatorial library can overcome many of these limitations. Hualiang Pi and John Helmann (DOI: 10.1039/c7mt00112f) describe iron(II) efflux systems in bacteria and point out that bacteria growing in iron-plentiful aerobic environments may require protection from redox damage. In this contribution, a number of iron efflux systems that offer such a protection for bacteria are also reviewed. An alternative method of minimizing iron toxicity is by scavenging and storing iron in a non-redox active form. Eshelman *et al.* (DOI: 10.1039/c7mt00042a) point out that two types of storage proteins exist in bacteria, the ferritins and the heme-containing bacterioferritins. They consider possible interactions between these two protective molecules in *Pseudomonas aeruginosa*.

Plant and Fungal Iron Biology

Comprehension of iron absorption in plants has a critical role in crop production. Connorton *et al.* (DOI: 10.1039/c7mt00136c) provide an overview of iron homeostasis in plants followed by a discussion on targets for traditional breeding of plants and biotechnological approaches. Biofortification of crops with iron is an attractive proposition, but a concept not without difficulties. Guerinot and co-workers (DOI: 10.1039/c7mt00152e) continue the discussion of emerging concepts by reporting on the influence of regulators for iron

deficiency responses of *Arabidopsis thaliana*. They point out that these control mechanisms are also present in rice and soybean and represent a potential target for enhancing the tolerance to iron deficiency in crop plants.

Hubert Haas and co-workers (DOI: 10.1039/c7mt00110j) present data relating to cytochrome P450 enzymes in the fungal pathogen *Aspergillus fumigatus*. This work is relevant to the development of resistance towards the ergosterol biosynthesis targeting antifungals.

Mammalian Iron Biology

This is a well studied subject and the present themed issue includes two excellent reviews on central issues relating to iron transport; one on hepcidin by Dominic Hare (DOI: 10.1039/c7mt00047b) and one on the transferrin receptors (i.e. Tfr1 and Tfr2) by Elena Gammella *et al.* (DOI: 10.1039/c7mt00143f). Hare points out that hepcidin provides a real-time indicator of iron requirements, in contrast to many of the more classical analytes. The quantification of this peptide in biological matrices is not simple and various methods are discussed in this review. Tfr1 is controlled at multiple levels and the latest advances in this field are discussed by Gammella *et al*. They compare the properties of Tfr1 and Tfr2 and suggest that Tfr1 acts as a vector for viral infections. A tentative link between duodenal cytochrome b ferric reductase and colorectal cancer risk is reported by Latunde-Dada and co-workers (DOI: 10.1039/c7mt00254h). Intracellular iron and heme trafficking is reviewed by Kafina and Paw (DOI: 10.1039/c7mt00103g). Several useful figures summarise iron metabolism in erythroid cells and describe the links between iron-sulfur cluster production and heme synthesis in mitochondria. The physico-chemical properties of manganese(II) and iron(II) are quite similar and this reflects their ability to share a number of divalent cation transporters. The influence of iron on manganese transport and toxicity is reviewed by Jaughan and co-workers (DOI: 10.1039/c7mt00079k), who indicate that a range of factors which influence iron metabolism may also have a role in manganese distribution and hence toxicity.

Guenter Weiss and co-workers (DOI: 10.1039/c7mt00177k) provide evidence for the effects of dietary iron on liver mitochondrial respiratory capacity. They suggest that tissue iron overload impaires mitochondrial function. This finding offers an explanation for the fatigue associated with iron overload syndromes. Over the past decade, epidemiological studies have connected allergy with a deficient iron-status and in this issue Roth-Walter *et al.* (DOI: 10.1039/c7mt00241f) report a complex interplay between iron, siderophores and immunomodulatory molecules such as lipocalin. Additionally, the contribution contains a useful list of microorganisms that are associated with allergy.

Treatment of Iron Associated Diseases

Sickle cell haemoglobin oxidises at a faster rate than normal HbA frequently resulting in the irreversible oxidation of βcys93 and the consequent loss of heme. Abdu Alayash and co-

workers (DOI: 10.1039/c7mt00104e) describe this phenomenon and its marked retardation by the disulfide TD-1, suggesting the involvement of βcys93. Nakashige and Nolan (DOI: 10.1039/c7mt00044h) discuss the role of calprotectin on the redox speciation of extracellular iron. By binding iron(II) with high affinity, it is suggested that calprotectin plays a physiological role in iron homeostasis at the host-pathogen interface during infection. Iron chelation therapy has been used to treat thalassemia for more than 50 years, and more recently such therapy has also demonstrated efficacy in the treatment of Parkinson's disease, both in animal models and clinical trials. Rachel Codd and co-workers (DOI: 10.1039/c7mt00039a) describe the synthesis of a series of desferrioxamine conjugates and their biological evaluation in a MPTP mouse model. Conjugation of an antioxidant or adamantane was found to result in neuroprotective effects – an important development in this emerging field. Yan *et al*. (DOI: 10.1039/c7mt00105c) describe the influence of heme-containing enzymes on immune suppression and suggest that inhibitors of a range of deoxygenases have potential to act synergistically in combination with immunotherapeutic agents.

Conclusions

Our aim in editing this themed issue is to provide postdoctoral researchers and PhD students with a wide range of reviews and original papers in the broad field of iron biology. Although divided into six sections, there is considerable overlap between the sections. The issue provides an opportunity for a person, new to the field, to gain access to a useful set of references and to some excellent up-to-date reviews.

References:

1. W. Maret and A. Wedd, *Binding, Transport and Storage of Metal Ions in Biological Cells*, RSC, 2014.
2. A. Sigel, H. Sigel and R. K. O. Sigel, *Interrelations between Essential Metal Ions and Human Diseases*, Springer Netherlands, 2013.
3. R. Crichton, *Iron Metabolism: From Molecular Mechanisms to Clinical Consequences, 4th Edition*, Wiley, 2016.
4. G. J. Anderson and G. D. McLaren, *Iron Physiology and Pathophysiology in Humans*, Humana Press, 2012.